

## Purified allogeneic hematopoietic stem cells as a platform for tolerance induction

### Grant Award Details

Purified allogeneic hematopoietic stem cells as a platform for tolerance induction

**Grant Type:** Transplantation Immunology

**Grant Number:** RM1-01733

**Project Objective:** The objectives of this proposal are to develop reagents that can replace toxic conditioning regimens for HSC transplantation by replacing them with reagents that target cell populations in recipients that constitute the immune and non-immune barriers to engraftment.

**Investigator:**

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<b>Institution:</b>	Stanford University
<b>Type:</b>	PI

**Disease Focus:** Blood Disorders, Immune Disease, Muscular Dystrophy

**Human Stem Cell Use:** Adult Stem Cell

**Award Value:** \$1,233,275

**Status:** Closed

### Progress Reports

**Reporting Period:** Year 1

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**Reporting Period:** Year 2

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**Reporting Period:** Year 3

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### Grant Application Details

**Application Title:** Purified allogeneic hematopoietic stem cells as a platform for tolerance induction

**Public Abstract:** Blood and immune cells originate and mature in the bone marrow. Bone marrow cells are mixtures of blood cells at different stages of development, and include rare populations of blood-forming stem cells. These stem cells are the only cells capable of generating the blood system for the life of an individual. Bone marrow transplants (BMT) have been performed > 50 years, to replace a diseased patient's blood system with that of a donor. Unfortunately, BMT have associated dangers which make the procedure high risk. Major risks include a syndrome called graft-versus-host disease (GvHD) which results when the donor's mature blood cells attack the organs of the host, and toxicity from the treatments (radiation and chemotherapy) required to permit the donor cells to take in the recipient. These risk factor limit the use of BMT to only immediate life-threatening diseases.

If made safer, BMT could cure many other debilitating diseases. In addition to being curative of blood cancers and non-malignant blood diseases (such as sickle-cell anemia), these transplants can cure autoimmune diseases, such as juvenile (type I) diabetes and multiple sclerosis. In addition, simultaneous BMT with organ transplants induces "tolerance" to the new organ, meaning the recipient will not reject the graft because the new blood system provides continuous proteins to re-train the recipient immune system not to attack it. This establishment of tolerance eliminates the need for drugs that suppress the immune system.

In efforts to make BMT safer, our research has focused on isolating the blood stem cells away from the other bone marrow cells because transplants of pure stem cells do not cause GvHD. We developed the methods to purify the blood stem cells from mouse and human blood forming sources and showed in mice that transplants of blood stem cells can cure autoimmune disease and induce tolerance to solid organ transplants. However, this technology has not been tested in human clinical trials because safer methods must be developed that permit the stem cells to engraft in recipients.

Our studies in mice show that we can replace the toxic drugs and radiation used to prepare recipients for BMT with non-toxic proteins that target the cells responsible for rejection of blood stem cells. The goal of this study is to translate this technology from mice to patient clinical trials. If successful, the studies will open the door to the use of blood stem cell transplants to the many thousands of patients who could benefit from this approach. The science behind achieving blood stem cell engraftment by the methods we propose look toward the future when blood stem cells and other tissues will be developed from pluripotent stem cells (ES, NT and iPS). We envision that the blood stem cells will induce tolerance to tissues derived from the same pluripotent stem cell line, in the same way that adult blood stem cells induce tolerance to organs from the same living donor.

**Statement of Benefit to California:**

The science and the preclinical pathway to induce human immune tolerance in patients with degenerative diseases so that new blood and tissue stem cells can regenerate their lost tissues: For stem cell biology to launch the era of regenerative medicine, stem cells capable of robust and specific regeneration upon transplantation must be found, and methods for safe patient administration must be developed. In the cases where cell donation cannot come from the host, immune responses will reject the donor stem cells. Successful transplants of blood-forming stem cells (HSC) leads to elimination immune cells that reject organ grafts from donors. While bone marrow or cord blood transplants contain immune cells called T cells that will attack the host in a potentially lethal graft against host immune reaction, purified HSC do not do this. Pluripotent stem cells (ES, NT, iPS) can make all cell types in the body and provide a shortcut to find tissue and organ stem cells. Just as co-transplants of adult HSC prevent rejection of organs from the same donor, co-transplants of HSC derived from pluripotent cells should protect tissues derived from the same pluripotent line. Attack by a patient's blood system against one's own organs cause the syndromes of autoimmune disease including juvenile diabetes, multiple sclerosis, and lupus. Transplanted HSC from donor mice genetically resistant to these diseases end the autoimmune attack permanently. We have in mice, substituted minimally toxic antibodies for toxic chemoradiotherapy to prepare the host for HSC transplants. Now it is time to take these advances to humans, with human immune cell and HSC-targeting antibodies.

Long-term potential benefits to the state of California and its residents: The justification for Proposition 71 was to establish in California centers of research not funded adequately in the areas of stem cell biology and regenerative medicine. This research, if successful, is the platform for the application of stem cell biology to regenerative medicine. The costs for long-term immune suppression to patients who receive organ transplants are enormous, both in terms of quality of life, even survival, and healthcare resources. Add to that the lifetime costs of insulin to treat juvenile diabetes, with the inevitable premature diseases of compromised blood vessels and organs, and the shortened lifespan of patients. Add to that the costs to lives and the healthcare system of lupus, of multiple sclerosis, of other autoimmune diseases like juvenile and adult rheumatoid arthritis and scleroderma, and of muscular dystrophy, to mention a few, and the value to Californians and people everywhere is obvious. If our studies are successful, and if the clinical trials were first done in California, our citizens will have the first chance at successful treatment. Further, if these studies are successful - new antibodies, if produced by CIRM funds, will generate royalties which eventually will return to the state.

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